Patent Office
Canberra

I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. PS 3032 for a patent by DENNIS JAMES BANNISTER as filed on 20 June 2002.

I further certify that the above application is now proceeding in the name of PACIFIC BIOLINK PTY LIMITED pursuant to the provisions of Section 113 of the Patents Act 1990.

COMMONWEALTH OF AUSTRALIA
AUSTRALIA
PATENT OFFICE

WITNESS my hand this
Second day of July 2003

J. Billingsley

JULIE BILLINGSLEY
TEAM LEADER EXAMINATION
SUPPORT AND SALES

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

PROTEIN BASED ORAL LUBRICANT

Technical Field

This invention relates to formulations containing phosphoprotein, designed for use as a mouth lubricant or as artificial saliva.

Background Art

Phosphoproteins of the prior art have been described for use in formulations for the treatment or prevention of diseases resulting from the action of bacteria in the oral cavity, for example, caries and gingivitis. However, the formulations of the prior art have not described formulations for use as an oral lubricant or as a saliva substitute.

The present invention provides formulations for use as an oral lubricant and for use as saliva substitutes for humans or animals, wherein said formulations comprise phosphoproteins. Further, the present invention provides formulations that are particularly useful for treating humans or animals with xerostomia.

'Xerostomia' or 'Dry Mouth' is not a disease, but it can be a symptom of certain diseases. Xerostomia can result from medical treatment or as a side effect of many medications. Many times xerostomia is caused by failure of the salivary glands to function normally. Xerostomia can cause health problems by affecting nutrition as well as psychological health. It can contribute to and increase the chances of contracting tooth decay and mouth infections. Causes of Xerostomia include:

a) Medications – Several hundred current medications can cause xerostomia. The major drug groups are antihypertensives and antidepressants. Analgesics, tranquilisers, diuretics, and antihistamines can also cause dry mouth.
b) Cancer Therapy – Chemotherapeutic drugs can change the flow and composition of saliva. Radiation treatment that is focused on or near the salivary gland can temporarily or permanently damage the salivary glands.
c) Systemic diseases – such as Sjogren's syndrome – an autoimmune disease, AIDS, diabetes, and Parkinson's disease.
d) Other conditions – such as bone marrow transplants, endocrine disorders, stress, anxiety, depression, and nutritional deficiencies may cause xerostomia.
e) Nerve Damage – Trauma to the head and neck area from surgery or wounds can damage the nerves that supply sensation to the mouth. While the salivary glands may be left intact, they cannot function normally without the nerves that signal them to produce saliva.
f) Conditions – Alzheimer's disease or stroke may change the ability to perceive oral sensations.

Erosion of tooth structure is defined as the superficial loss of dental hard tissue due to a chemical process not involving bacteria. There can be a variety of chemical factors involved in erosion as follows: food, drink, drugs, regurgitation of gastric acid, gastric reflux, and vomiting. Tooth erosion and loss of teeth is common amongst humans or animals with dysfunctional salivary glands and xerostomia. Dysfunctional salivary glands can occur, for example, as a result of radiotherapy in the throat area.

Object of the Invention

An object of the invention is to provide a phosphoprotein based formulation for use as an oral lubricant.

Disclosure of the Invention

According to a first embodiment of the invention, there is provided a formulation for use as an oral lubricant or as artificial saliva in humans or animals, wherein said formulation comprised a solution or suspension of at least one type of phosphoprotein in water.

Typically, the phosphoprotein is a casein phosphoprotein or salt thereof, that may be present in the formulation as a mixture of any two or more of the proteins outlined below.

Typically, the isolated and purified casein protein may comprise a casein protein as disclosed in Whitney, R. Proteins of Milk. In: Fundamentals of Dairy Chemistry 3rd Edn. (1988) (ed. N.P. Wong), Van Nostrand Reinhold, NY, USA, pages: 82-91, the disclosure of which is incorporated herein by reference. More typically, the casein protein is selected from the group consisting of: α-casein, β-casein, κ-casein, and mixtures thereof. Yet aeven more typically, the casein protein is selected from the group consisting of:

A. α_{s1}-Caseins
1. α_{s1}-Casein X^a-8P (genetic variants-A, B, C, D-9P, and E)
2. α_{s1}-Casein X^a-9P (genetic variants-A, B, C, D-10P, and E)
3. α_{s1}-Casein fragments

B. α_{s2}-Caseins
1. α_{s2}-Casein X^a-10P (genetic variants-A, B, C-9P, and D-7P)
2. α_{s2}-Casein X^a-11P (genetic variants-A, B, C-10P, and D-8P)
3. α_{s2}-Casein X^a-12P (genetic variants-A, B, C-11P, and D-9P)
4. α_{s2}-Casein X^a-13P (genetic variants-A, B, C-12P, and D-10P)

C. β-Caseins
1. β-Casein X^a-5P (genetic variants-A^1, A^2, A^3, B, C-4P, D-4P, and E)
2. β-Casein X^a-1P (f 29-209) (genetic variants-A^1, A^2, A^3, and B)
3. β-Casein X^a-(f 106-209) (genetic variants-A^1, A^3, and B)
4. β-Casein X^a-(f 108-209) (genetic variants-A and B)
5. β-Casein X^a-4P (f 1-28)[b]
6. β-Casein X^a-5P (f 1-105)[b]
7. β-Casein X^a-5P (f 1-107)[b]
8. β-Casein X^a-1P (f 29-105)[b]
9. β-Casein X^a-1P (f 29-107)[b]

D. κ-Caseins
1. κ-Casein X^a-1P (genetic variants-A and B)
2. Minor κ-Caseins X^a-1, -2, -3, etc. (genetic variants-A and B)

Typically, the casein protein may be isolated and purified from bovine, ovine or caprine milk. More typically, the casein protein for use in the invention is any commercially available casein protein.

Typically, the protein within the formulation is designed as an alternative to the protein found in natural saliva.

Typically, the protein statherin could also be used if at some stage this becomes commercially viable.

Typically, the formulation of the present invention also includes a phosphatase inhibitor. More typically, the phosphatase inhibitor is selected from the group consisting of: fluoride ions, anionic polymers, and divalent and trivalent metal ions.

Note that unless otherwise stated, all percentages of components of the formulation are by weight, based on the total weight of the formulation.

Typically, the amount of protein in the formulation is between about 0.0001 and about 60%. More typically, the amount of protein present in the formulation is between 0.01 and 25%. Even more typically, the amount of protein in the formulation is between 0.5 and 20%.

Typically, the formulation may also contain calcium phosphate in the form of a complex with the protein.

Typically, the amount of calcium present in the formulation is between about 0.0001 and about 25%. More typically, the amount of calcium present in the formulation is between 0.001 and 0.5%. Even more typically, the amount of calcium present in the formulation is between 0.002 and 0.01%.

Typically, the amount of orthophosphate present in the formulation is between about 0.0001 and about 25%. More typically, the amount of phosphate present in the formulation is between 0.001 and 0.5%. Even more typically, the amount of phosphate present in the formulation is between 0.002 and 0.01%.

Typically, any component that is found in natural saliva may also be a component of the oral lubricant of this invention. Typically, saliva constituents are selected from the group consisting of sodium, potassium, chlorides, fluorides, phosphates, bicarbonates, oxygen, carbon dioxide, urea, enzymes such as ptyalin, maltase, and amylase, and proteins such as mucin, globulin, albumen, and statherin.

Typically, the pH of the formulation is between 4.7 and 10. More typically, the pH of the formulation is between 6 and 7.5.

Typically, the formulation is sterile. More typically, the formulation is pasteurized. This is to eliminate or reduce bacterial contamination that could cause odorous bacterial breakdown or cause illness in the recipient of the saliva.

The functions of the artificial saliva include those for natural saliva as follows:
Wash away food debris and plaque from the teeth to help prevent caries.
Limit the growth of bacteria that cause tooth decay, mouth odor, and other mouth infections.
Bathe the teeth and supply minerals such as calcium and phosphate that allow remineralisation of tooth structure.
Lubricate foods so they may be swallowed more easily.
Moisten the skin inside the mouth to make chewing and speaking easier.
Providing enzymes that aid in digestion.
Help us enjoy foods by aiding in the "tasting" process.

Typically, the formulation may contain at least one anti-microbial agent. Typically, any anti-microbial agent found in commerce is also suitable for use in the formulation of the present invention.

Typically, the anti-microbial agent may be selected from the group consisting of: halogenated diphenyl ethers, such as: 2,4,4-trichloro-2-hydroxy-diphenyl ether (triclosan); phenolic compounds, including phenol and its homologues, such as: 2-methyl-phenol, 3-methyl-phenol, 4-methyl phenol, 4-ethyl phenol, 2,4-dimethyl-phenol,

3,4-dimethyl-phenol, 2,6-dimethyl-phenol, 2,2-methylene bis (4-chloro-6-bromo-phenol); mono- and poly-alkyl and aromatic halophenols, including p-chlorophenols such as: methyl-p-chlorophenol, ethyl-p-chlorophenol, n-propyl-p-chlorophenol, n-butyl-chlorophenol; -o-chlorophenols; p-bromophenols; -o-bromophenols; resorcinol and its derivatives, such as: n-methyl hexyl resorcinol; bisphenolic compounds and halogenated carbanilides.

More typically, the anti-microbial agent may be selected from the group consisting of: glycerol, ethanol, sorbitol, mannitol, sodium benzoate, methyl-p-hydroxy benzoate, ethyl-p-hydroxybenzoate, N-propyl p-hydroxybenzoate, butyl-p-hydroxybenzoate, phenoxy ethanol and quaternary ammonium salts, such as benzethonium chloride, and diisobutyl-phenoxyethoxyethyl dimethyl benzyl ammonium chloride.

Other types of anti-microbial agents may include amidines, such as substituted guanidine, including chlorhexidine, and other known bis-biguanidines; and cationic tertiary amines.

Typically, the amount of ethanol present in the formulation is between about 0.05 and about 20%. More typically, the amount of ethanol present in the formulation is between about 0.5 and about 10%. Even more typically, the amount of ethanol present in the formulation is between about 1 and about 8%. Yet even more typically, the amount of ethanol present in the formulation is between about 2 and about 6%.

Typically, the formulation as defined in accordance with the first embodiment of the invention is capable of accepting a suitable amount of a viscosity modifier. The viscosity modifier is used to regulate the viscosity of the oral lubricant, wherein the biological activity of the protein Typically, the viscosity of the formulation is similar to that of natural saliva, but may also be a thixotropic gel that liquefies under shear.

The viscosity modifier may be selected from the natural polymers: proteins, mucin, including synthetic and natural mucin, glycoproteins, hydrolysed proteins, globulin, albumin, statherin, alginate, cellulose and cellulose derivatives. The viscosity modifier may be selected from the synthetic polymer: carboxymethyl cellulose.

Other suitable viscosity modifiers include irish moss, gum tragacanth, starch, polyvinylpyrrolidone, hydroxyethylpropylcellulose, hydroxybutyl methyl cellulose, hydroxypropyl methyl cellulose, hydroxy ethyl cellulose (e.g. available as Natrosol), sodium carboxymethyl cellulose, colloidal silica such as finely ground Syloid, laponite (any form of laponite, such as laponite DF), hectorite, calcium montmorillonite, acid activated bleaching earth and palygorskite.

Typically, casein is used as a viscosity modifier.

Typically, the formulation of the first embodiment of the invention can be used as a mouthwash, and delivered to the oral cavity using any type of vessel, or in the form of a spray. The mouthwash is swallowed or spit out after application to the oral cavity.

More typically, the formulation is delivered to the oral cavity from a reservoir of artificial saliva, via a tube that is implanted in the body. The reservoir may be stored inside or outside the body. The rate of delivery of the formulation to the oral cavity may be controlled by an electric pump. The pump speed may be adjusted by the operator.

Typically, the rate of delivery of the artificial saliva from the reservoir to the oral cavity is between about 0.01 to about 100 ml/minute. More typically, the rate of delivery of the artificial saliva from the reservoir to the oral cavity is between about 0.05 to about

10 ml/minute.

Any suitable flavouring or sweetening material may also be employed. Examples of suitable flavouring constituents are flavouring oils. For example, oil of spearmint, peppermint, wintergreen, sassafras, clove, sage, eucalytus, marjoram, cinnamon, lemon, and orange, and methyl salicylate. Suitable sweetening agents include sucrose, lactose, maltose, dextrose, laevulose, sorbitol, xylitol, d-tryptophan, dihydrochalcones, sodium cyclamate, perillartine, APM (aspartylphenylalanine, methyl ether), saccharine and the like. Suitably, flavouring and sweetening agents may together comprise from about 0.1 to 10% by weight or more of the preparation, and more typically, from about 0.1% to 5% by weight or more of the preparation.

Humectants contemplated for use in the formulations of the present invention include: glycerol, polyol, sorbitol, polyethylene glycols, propylene glycol, hydrogenated partially hydrolysed polysaccharides and the like. The humectants are generally present in amounts of from 0 to 80%, typically 5 to 70% by weight. Variuos other materials may be incorporated in the oral formulations of the present invention, such as preservatives, silicones, chlorophyll compounds, anti-calculus agents, anti-caries agents, and/or ammoniated material such as urea, diammonium phosphate, and mixtures thereof. These adjuvants, where present, are incorporated in the preparations in amounts which do not substantially adversely affect the properties and characteristics desired.

According to a second embodiment of the invention, the formulation may be used to provide vitamins and minerals to humans or animals.

Typically, the vitamins may be one or more of any type found in the body of humans or animals. Vitamins may be selected from the group consisting of: Vitamin A, Vitamin C, Vitamin D, Vitamin D_1, Vitamin D_3, Vitamin E, Vitamin K, Vitamin K_1, Vitamin B complex, Vitamin B_1, Vitamin B_2, Vitamin B_6, Vitamin B_{12}, folate, cytamen, and nicotinate.

Typically, the minerals may be one or more selected from the group consisting of: Calcium, phosphate, fluoride, magnesium, barium, strontium, zinc, iron, nickel, aluminium, copper, tin, fluorophosphate, cobalt, sodium, potassium, chloride, bromide, iodide and oxide.

According to a third embodiment of the invention, the formulation may be used for the delivery of any drug that may be taken orally. Typically, the drug may stimulate the production of natural saliva. Typically, the drug designed to stimulate the production of natural saliva may be selected from the group consisting of: Pilocarpine, Salogen and Biotene.

According to a fourth embodiment of the invention, the formulation of the first embodiment of the invention may be spray-dried to a powder form, for use as a saliva substitute or to supplement the calcium and phosphate levels in the oral cavity of humans or animals with reduced saliva production or have saliva with low concentrations of calcium and phosphate. Typically, the spray-dried formulation is added to confectionary such as chewing gum, lozenges, sweets and the like.

Formulations of the present invention can be incorporated in lozenges, or in chewing gum or other products, for example by stirring in a pre-dried form of the formulation in solid form into a warm gum base vehicle. Typically of these include jelotone, rubber latex, vinylite resins, and desirably with conventional plasticisers or

softeners, sugar or other sweeteners or carbohydrates such as glucose, sorbitol and the like.

More typically, formulations in accordance with the first embodiment of the invention may be dried, for example, by spray drying, and then added to substances, such as lozenges, chewing gums, carbonated beverages, salt, sugar, artificial sweeteners, baked goods, toothpaste, mouthwash and other oral hygiene products.

A preferred form of the present invention is a chewing gum. The chewing gum may be made from any gum base composition well known in the art and includes those gum bases utilised for conventional chewing gums and bubblegums. Gum bases typically include a polymeric material and may comprise elastomers, resins, polyvinyl acetates, waxes, fats, oils, emulsifiers, fillers and antioxidants.

Typically, a chewing gum in accordance with the present invention may comprise ingredients present in amounts selected from the following ranges: typically, between about 10 to about 80%, more typically, between about 25 to about 80%, even more typically, between about 40 to about 80%, of a gum base; typically, about 0.1 to about 40%, more typically, about 0.1 to about 25%, even more typically, about 1 to about 10% of a pre-dried form of the formulation; typically, between about 5 to about 70%, more typically, between about 10 to about 50%, even more typically, between about 25 to about 40% of a water-soluble bulking ingredient; typically, between 0 to about 5% of a flavourant, more typically, between about 0 to about 3.5% of a flavourant; even more typically, between 0 to about 2% of a flavourant; typically, between 0 to about 0.2%, more typically, between 0 to about 0.1%, even more typically, between 0 to about 0.05% of a colourant; typically, between 0 to about 20%, more typically, between 0 to about 15%, even more typically, between 0 to about 10% of an abrasive; typically, between 0 to about 3%, more typically, between 0 to about 2%, even more typically, between 0 to about 1% of a surfactant; and typically, between 0 to about 3%, more typically, between 0 to about 2%, even more typically, between 0 to about 1% of a fluoridating agent.

As outlined above, unless otherwise stated all percentages of components of the chewing gum form of the formulation are by weight, based on the total weight of the chewing gum composition.

Typically, the chewing gum may be any variety of different chewing gum types including low and high moisture, sugar or sugarless, wax-containing or wax free, low calorie, and the like, and can contain any constituent of the healthy saliva of humans or animals.

In general, a chewing gum product generally consists of a water-insoluble gum base, a water-soluble portion, and flavours. The water-soluble portion dissipates over a period of time, and the gum base portion is retained during mastication. Further, a conventional chewing gum base usually contains an elastomer, an elasatomer solvent, and various other ingredients such as fillers, softeners, plasticisers and emulsifiers.

Typically, chewing gum base elastomers include: chicle, jelotong, balata, crown gum, guttapercha, sorva, lechi capsi, crown gum, nispero, rosidinha, perillo, niger gutta, tunu, gutta kay, pendare, leche de vaca, chiquibul, and the like, butadiene-styrene copolymer, polyisobutylene, isobutylene-isoprene copolymer, polyethylene, and the like, and mixtures thereof. More typically, the amount of elastomers employed in the gum base composition varies greatly depending upon factors such as the type of gum base used, the consistency of the gum base composition desired, and the other components

used in the composition to make the final chewing gum product. Even more typically, the elastomer is present in the gum base composition in an amount of between any one of the following: about 15% to about 60%; about 15% to about 30%; or about 25% to about 30%.

Typically, the elastomer solvents are also present in the gum base composition, wherein they act in softening or plasticising the elastomer component. Chewing gum base elastomer solvents include pentaerythritol ester of wood rosin, glycerol ester of polymerised rosin, partially hydrogenated methyl ester of rosin, and the like. More typically, the elastomer solvent may be employed in the gum base composition in an amount of from about 2% to about 40%, and even more typically, from about 7% to about 15%.

Typically, waxes, fats/oils are also present in the gum base composition, wherein they act to improve the elasticity of the gum base. Waxes can provide a soft or firm chew, influence the flavour release and provide bulkiness and smoothness to the gum base. The fats, oils and waxes may be used individually or in combination in the gum base, and may be of mineral, animal, vegetable or synthetic origin. Examples of waxes include paraffin, microcrystalline waxes, polyethylene wax, paraffin wax, beeswax, carnauba wax, microcrystalline wax, carnauba wax, candellila wax, rice bran wax, esparto wax, flax wax, sugarcane wax, and synthetic waxes.

Further, examples of suitable oils and fats useable in gum compositions include hydrogenated or partially hydorgenated vegetable or animal fats, and these may be selected from the group consisting of: cottonseed oil, soybean oil, coconut oil, palm kernel oil, beef tallow, hydrogenated tallow, lard, cocoa butter, lanolin and the like, fatty acids such as palmitic, oleic, stearic, linoleic, lauric, myristic, caproic, caprylic, decanoic or esters and salts as sodium stearate and potassium stearate. More typically, these ingredients when used are generally present in amounts up to about 8%, and even more typically up to about 4%.

Generally, the gum base composition may also include effective amounts of fillers or bulking agents, which act to increase firmness and bulk and influence the texture and the flavour release of the chewing gum. Typically, fillers may include organic and inorganic compounds (mineral adjuvants) such as calcium carbonate, magnesium carbonate, ground limestone, magnesium silicate, calcium phosphate, cellulose polymers, clay, alumina, aluminium hydroxide, aluminium silicate, talc, tricalcium phosphate, dicalcium phosphate, and mixtures thereof.

More typically, the amount of the filler present in the gum base composition in an amount from about 1% to about 40%, still more typically, from about 5% to about 20%.

Chewing gum compositions generally include sugar and sugar alcohol sweeteners, having a range in sweetening intensity, which may also act as bulking agents. For example, in sugarless gum compositions, a sweetening agent, such as sorbitol or other sugar alcohol, may act as a bulking agent.

Typically, sugar based sweetening /bulking agents include: monosaccharides, disaccharides and polysaccharides. More typically, the polysaccharides may be selected from the group consisting of: xylose, ribulose, glucose (dextrose), mannose galactose, fructose (levulose), sucrose, maltose, and mixtures thereof. Further, typical sugar alcohol bulking agents include sorbitol, xylitol, mannitol, galactitol, maltitol, mixture of alpha-D-glucopyranosyl-1 6-mannitol and alpha-D-glucopyranosyl-1 6-sorbitol, maltodextrins,

hydrogenated starch hydrolysates; hydorgenated hexoses; hydrogenated disaccharides; and the like, and mixtures thereof. Even more typically, the bulking agents/sweeteners may be present in an amount of from about 15% to about 90%, and still more typically, in an amount from about 25% to about 65%, and even more typically, from about 30% to about 50%.

More typically, the chewing gum compositions may also include a high intensity sweetening agent. More typically, the agent is selected from the group consisting of: dihydrochalcone, monellin, steviosides, glycyrrhizin, dihydroflavenol, and L-aminodicarboxylic acid, aminoalkenoic acid ester amindes, saccharin and salts thereof, 3,4-dihydro-6-methyl-1, 2, 3-oxathiazine-4-one-2,2-dioxide and salts thereof, and L-aspartic acid derived sweeteners, sucha as Aspartame, Alitame, and derivatives of chlorodeoxysucrose or chlorodeoxygalactosucrose.

Typically, the amount of sweetener employed in the chewing gum composition will vary with the sweetener selected for a particular chewing gum and the level of sweetness desired. More typically, the sweeteners are usually present in an amount from about 1% to about 70% and still more typically, in an amount from about 40% to about 50%. Still more typically, the intense sweeteners are usually used in an amount of up to about 1%, and even more typically, from about 0.05% to about 0.4%.

Typically, chewing gum composition may also contain a flavouring agent, and more typically, the flavouring agent is in an amount from about 0.02% to about 5%.

Typically, chewing gum composition may also comprise additives selected from the group consisting of: colouring agents such as: titanium dioxide, incorporated in amounts up to about 2%; thickening agents such as; methyl cellulose, alginates, carrageenan, xanthan gum, gelatin, carob, tragacanth, and locust bean, and fillers.

Typically, in the lozenge according to the present invention, the topical vehicle or carrier in a tablet of lozenge is a solid water-soluble polyhydric alcohol (polyol) such as mannitol, xylotil, sorbitol, malitol, a hydrogenated starch hydrolysate, Lycasin, hydrogenated glucose, hydrogenated disaccharides, and hydrogenated polysaccharides in an amount of about 90 to 98% by weight of the total composition. Solid salts such as sodium bicarbonate, sodium chloride, potassium bicarbonate or potassium chloride may totally or partially replace the polyol carrier.

According to a fifth embodiment of the invention, there is provided the formulation in accordance with the first embodiment of the invention, when used in the treatment and/or prevention of tooth erosion in humans or animals in need of said treatment and/or prevention.

According to a sixth embodiment of the invention, there is provided use of the formulation in accordance with the first embodiment of the invention, in the preparation of a medicament for the treatment and/or prevention of tooth erosion in humans or animals in need of said treatment and/or prevention.

Typically, the treatment and/or prevention of tooth erosion involves release of calcium, phosphate and/or fluorophosphate ions from the protein and/or peptide-amorphous calcium phosphate and/or fluorophosphate complexes.

Typically, the prevention of tooth erosion involves the casein phosphoprotein precipitating at pH 4.6 or lower, providing an insoluble lining on the teeth, and therefore preventing release of dental hard tissue.

Typically, in accordance with the first embodiment of the invention, the problems associated with xerostomia including tooth erosion, are treated and/or prevented by application of a thixotropic gel, and preferably applied by applying the gel regularly within the oral cavity, thereby applying the formulation to the teeth and gums. Typically, the thixotropic gel formulation is applied to the teeth and gums in a mouth guard for at least two minutes and up to one hour each day, preferably for a duration of two weeks up to 16 weeks or more, and even up to lifetime.

Typically, the formulation is applied in the form of a toothpaste. Typically, abrasives used in the formulations of the present invention, may include alumina and hydrates thereof, such as amorphous silica, alpha alumina trihydrate, magnesium trisilicate, dicalcium phosphate, magnesium carbonate, aluminosilicate, such as clacined aluminium silicate and aluminium silicate, calcium carbonate, zirconium silicate, polymethylmethacrylate. powdered polyethylene, polypropylene, polypropylene, silica xerogels, hydrogels and aerogels and the like. Also suitable as abrasive agents are calcium pyrophosphate, insoluble sodium metaphosphate, calcium metaphosphate, dicalcium orthophosphate, particulate hydroxyapatite and the like. Depending on the form which the oral formulation is to take, the abrasive may be present in an amount of from about 0 to about 70% by weight, typically about 1 to about 70% by weight, more typically from about 10 to about 70% by weight, particularly for toothpastes.

Best Modes and Other Modes of Carrying out the Invention

Typically, the preferred formulation of the present invention falls within the following ranges, wherein all proportions are expressed by weight:

Protein	0.0001 to 60%
Water	Up to 100%

Typically, the preferred formulation of the present invention falls within the following ranges:

Protein	0.001 to 20%
Calcium	0.0001 to 5%
Phosphate	0.0001 to 5%
Water	Up to 100%

A more preferred formulation of the present invention falls within the following ranges:

Protein	0.01 to 20%
Calcium	0.002 to 0.01%
Phosphate	0.002 to 0.01%
Water	Up to 100%

A further formulation of the present invention falls within the following ranges:

Protein	0.01 to 20%
Calcium	0.002 to 0.01%
Phosphate	0.002 to 0.01%
Ethanol	0.05 to 20%
Water	Up to 100%

Typically, a formulation of the present invention may also contain a viscosity modifier, within the following ranges:

Protein	0.01 to 20%
Calcium	0.002 to 0.01%
Phosphate	0.002 to 0.01%
Mucin	0.001 to 20%
Water	Up to 100%

Typically, a formulation of the present invention may contain a Vitamin, within the following ranges:

Protein	0.01 to 20%
Calcium	0.002 to 0.01%
Phosphate	0.002 to 0.01%
Vitamin D	0.0001 to 0.1%
Water	Up to 100%

Typically, a formulation of the present invention may contain extra mineral, within the following ranges:

Protein	0.01 to 20%
Calcium	0.002 to 0.01%
Phosphate	0.002 to 0.01%
Magnesium chloride	0.0001 to 0.1%
Water	Up to 100%

Typically, a formulation of the present invention may contain enzymes, within the following ranges:

Protein	0.01 to 20%
Calcium	0.002 to 0.01%
Phosphate	0.002 to 0.01%
Amylase	0.00001 to 0.01%
Water	Up to 100%

Typically, a formulation of the present invention may contain a saliva stimulator, within the following ranges:

Protein	0.01 to 20%
Calcium	0.002 to 0.01%
Phosphate	0.002 to 0.01%
Ethanol	0.5 to 20%
Pilocarpine	0.001 to 0.1%
Water	Up to 100%

A specific artificial saliva formulation in accordance with the present invention includes:

Protein	0.5%
Disodium phosphate	0.02%
Calcium chloride dihydrate	0.02%
Water	Up to 100%
Adjusted to pH 7.0 with 1N NaOH	

Typically, a formulation of the present invention may be spray dried to form a powder, within the following ranges:

Protein	10 to 40%
Phosphate	0.1 to 10%
Calcium	0.1 to 10%
Water	Up to 100%
Adjusted to pH 7.5 with 1N NaOH	

A spray dried powder of the above formulation is obtained from a Niro Production Minor Spray Drier (Niro Australia Pty. Ltd, Blackburn VIC, Australia), with an inlet temperature of about 200°C, and a flow rate that controlled the outlet temperature to about 85°C.

The resultant spray-dried powder formulation in accordance with the present invention is then added to vehicles such as: chewing gum, lozenges, foods, beverages, confectionary, pharmaceutical compositions, toothpaste creams or gels, or mouthwashes.

For example, a formulation of the present invention, in the form of a chewing gum may be prepared as follows:

A 2% by weight formulation in accordance with the first embodiment of the invention present in the form of a chewing gum comprising: 88% of a gum base, 2% of a spray-dreid formulation in accordance with the first embodiment of the invention, wherein the spray dried formulation comprises 4% calcium phosphate and 96% hydrolysed casein; 7% of a water-soluble bulking ingredient ; 2% of a flavourant ingredient; and about 0.2% of a colourant; was prepared according to the following.

The gum base may comprise: elastomers, such as crown gum, in an amount of 25 to 55%, elastomer solvents, such as rosin esters, in an amount of 5-25%, waxes, such as paraffin, in an amount of 5-10%, and fillers, such as calcium cabonate in an amount of 15%.

The manner in which the gum base components are admixed is not critical and is performed using standard techniques and apparatus known to those skilled in the art and may be a traditional batch-type process or any extrusion-type process. In a typical method, an elastomer is admixed with an elastomer solvent and/or a plasticiser and/or an emulsifier and agitated for a period of time usually from 1 to 30 minutes. Afetr blending is complete, the remaining ingredients may be added in bulk, incrementally, or stepwise while mixing until a homogeneous mass is obtained. The process may take from 15 minutes to 6 hours in a traditional batch type process. The final mass temperature may vary from 40°C to 175°C. The final homogeneous mass is discharged from the mixer and allowed to cool and thereafter the gum base composition is incorporated into a chewing gum composition.

The amount of gum base employed in the chewing gum composition will vary depending on such factors as the type of product desired, the type of gum base used, the consistency desired, and the other components used to make the final chewing gum product.

Once prepared, the gum base together with the 2% by weight formulation in accordance with the first embodiment of the invention may be formulated to prepare a wide variety of chewing gum compositions, wherein the chewing gum compositions are prepared using standard techniques and equipment known to those skilled in the art. The apparatus useful in accordance with the present invention comprises mixing and heating

apparatus well known in the chewing gum manufacturing arts, and therefore the selection of the specific apparatus would be readily apparent to the person skilled in the art.

Typically, a spray-dried formulation of the present invention may be incorporated into vehicles such as: chewing gum, lozenges, foods, beverages, confectionary, pharmaceutical compositions, toothpaste creams or gels, or mouthwashes, whereby the formulation of the present invention is administered at a rate of between 1 to 100g per kg of dry weight of the vehicle, such as food. More typically, a spray-dried formulation of the present invention is administered at a rate of between 1 to 75g per kg of dry weight of food. Even more typically, a spray-dried formulation of the present invention is administered at a rate of between 1 to 50g per kg of dry weight of food. Yet even more typically, a spray dried formulation of the present invention is administered at a rate of between 5 and 40g per kg of dry weight of food. Yet still more typically, a spray-dried formulation of the present invention is administered at a rate of between 5 to 20g per kg of dry weight of food.

The invention will now be described in greater detail by reference to specific Examples, which should not be construed as limiting on the scope thereof.

Examples

The sodium caseinate used in the following examples were supplied by New Zealand Milk Products (Australia) Pty. Ltd. 30 Frank St., Wetherill Park, NSW, 2164. The 'phosphopeptide' was isolated using the method disclosed in AU9216468.

Example 1

An oral lubricant formulation in accordance with the present invention was prepared according to the following:

Add 0.6% by weight sodium caseinate to 99.2% by weight water, and 0.2% by weight 1N sodium hydroxide, stirring with an overhead stirrer until all the caseinate had dispersed. Then pasteurise.

Example 2

An oral lubricant formulation in accordance with the present invention was prepared according to the following:

1) Part A: Adding 0.6% by weight sodium caseinate, 0.02% by weight disodium phosphate, to 99.38% by weight water, and 0.2% by weight 1N sodium hydroxide, stirring with an overhead stirrer until all the caseinate had dispersed.
2) Part B: Dissolving 0.4% by weight calcium chloride dihydrate in 99.6% by weight water.
3) Whilst stirring 950 grams of Part A, add dropwise 50 grams of Part B, and continue stirring with an overhead mixer for thirty minutes.
4) Pasteurising.

Example 3

An oral lubricant formulation containing an anti-microbial constituent in accordance with the present invention was prepared according to the following:

1) Part A: Adding 0.1% by weight phosphopeptide, 0.5% by weight sodium caseinate, 0.04% by weight disodium phosphate, to 5% by weight ethanol, 0.2% by weight 1N sodium hydroxide, and 94.16% by weight water, and stirring until all components had dispersed.
2) Part B: Dissolving 0.8% by weight calcium chloride dihydrate in 99.2% by weight water.

3) Whilst stirring 950 grams of Part A, add dropwise 50 grams of Part B, and continue stirring with an overhead mixer for thirty minutes.

Example 4

An oral lubricant or artificial saliva formulation containing a viscosity modifier according to the present invention was prepared according to the following:

1) Part A: Adding 0.3% by weight sodium caseinate phosphoprotein, 0.3% by weight hydrolysed casein, 0.02% by weight disodium phosphate, and 0.01% by weight mucin, to 99.17% by weight water and 0.2% by weight 1N sodium hydroxide, and stirring until all components had dispersed.

2) Part B: Dissolving 0.4% by weight calcium chloride dihydrate in 99.6% by weight water.

3) Whilst stirring 950 grams of Part A, add dropwise 50 grams of Part B, and continue stirring with an overhead mixer for thirty minutes.

4) Pasteurising.

Example 5

An artificial saliva formulation containing a Vitamin according to the present invention was prepared according to the following:

1) Part A: Adding 0.6% by weight phosphopeptide, 0.04% by weight disodium phosphate, and 0.01% Vitamin C, to 0.2% by weight 1N sodium hydroxide and 99.15% by weight water, and stirring until all components had dispersed.

2) Part B: Dissolving 0.8% by weight calcium chloride dihydrate in 99.2% water.

3) Whilst stirring 950 grams of Part A, add dropwise 50 grams of Part B, and continue stirring with an overhead mixer for thirty minutes.

4) Pasteurising.

Example 6

An artificial saliva formulation containing additional minerals according to the present invention was prepared according to the following:

1) Part A: Adding 0.1% by weight phosphopeptide, 0.5% by weight sodium caseinate, and 0.02% by weight disodium phosphate, to 0.2% by weight 1N sodium hydroxide, and 99.18% by weight water, and stirring until all components had dispersed.

2) Part B: Dissolving 0.4% by weight calcium chloride dihydrate, and 0.2% by weight magnesium chloride in 99.4% by weight water.

3) Whilst stirring 950 grams of Part A, add dropwise 50 grams of Part B, and continue stirring with an overhead mixer for thirty minutes.

4) Pasteurising.

Example 7

An artificial saliva formulation containing an enzyme according to the present invention was prepared according to the following:

1) Part A: Adding 7.0 grams by weight sodium caseinate, 0.0001% by weight amylase, and 0.02% by weight disodium phosphate, to 1.0% by weight 1N sodium hydroxide, and 91.9799% by weight water, and stirring until all components had dispersed.

2) Part B: Dissolving 0.4% by weight calcium chloride dihydrate in 99.6% by weight water.

3) Whilst stirring 950 grams of Part A, add dropwise 50 grams of Part B, and continue stirring with an overhead mixer for thirty minutes.

4) Pasteurising.

Example 8

An artificial saliva formulation containing a saliva stimulator according to the present invention was prepared according to the following:

1) Part A: Adding 0.1% by weight phosphopeptide, 0.5% by weight sodium caseinate, 0.04% by weight disodium phosphate, to 5% by weight ethanol, 0.2% by weight 1N sodium hydroxide, 0.1% by weight Pilocarpine, and 94.06% by weight water, and stirring until all components had dispersed.

2) Part B: Dissolving 0.8% by weight calcium chloride dihydrate in 99.2% by weight water.

3) Whilst stirring 950 grams of Part A, add dropwise 50 grams of Part B, and continue stirring with an overhead mixer for thirty minutes.

Example 9

An artificial saliva formulation that is suitable for delivery to the oral cavity via an implanted tube according to the present invention was prepared according to the following:

1) Part A: Adding 7.0 grams by weight sodium caseinate, 0.0001% by weight amylase, and 0.02% by weight disodium phosphate, to 1.0% by weight 1N sodium hydroxide, and 91.9799% by weight water, and stirring until all components had dispersed.

2) Part B: Dissolving 0.4% by weight calcium chloride dihydrate in 99.6% by weight water.

3) Whilst stirring 950 grams of Part A, add dropwise 50 grams of Part B, and continue stirring with an overhead mixer for thirty minutes.

4) Pasteurising.

Example 10

A formulation in accordance with the present invention for the use in the treatment and/or prevention of tooth erosion was prepared according to the following:

1) Part A: Adding 0.1% by weight phosphopeptide, 0.5% by weight sodium caseinate, 0.04% by weight disodium phosphate, to 5% by weight ethanol, 0.2% by weight 1N sodium hydroxide, and 94.16% by weight water, and stirring until all components had dispersed.

2) Part B: Dissolving 0.8% by weight calcium chloride dihydrate in 99.2% by weight water.

3) Whilst stirring 950 grams of Part A, add dropwise 50 grams of Part B, and continue stirring with an overhead mixer for thirty minutes.

Example 11

A spray dried form of the protein and/or peptide-calcium phosphate complex according to the present invention was prepared according to the following:

1) Part A: Adding 23.0% by weight hydrolysed casein, 1.1% by weight disodium phosphate, to 74.4% by weight water and 1.5% by weight 4N sodium hydroxide, and stirring until all components had dispersed.

2) Part B: Dissolving 10.0% by weight calcium chloride dihydrate in 90.0% by weight water.

3) Whilst stirring 950 grams of Part A, add dropwise 50 grams of Part B, and continue stirring with an overhead mixer for thirty minutes.